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Delineation of a Clinical Syndrome Caused by Mosaic Trisomy 15

Erica M. Bühler, Georg Bienz, Eliane Straumann, and Nemya Bösch
Department of Medical Genetics, University Children's Hospital, Basel, Switzerland

We report on a boy with mosaic trisomy 15. The clinical manifestations are compared with those of the few cases reported up to now. A clinical syndrome is delineated consisting of a characteristic shape of the nose and other minor craniofacial anomalies, as well as typical deformities of the hands and feet. Different degrees of mosaicism may explain the more or less severe manifestations in individual patients. © 1996 Wiley-Liss, Inc.

KEY WORDS: **trisomy 15, mosaic trisomy 15, tissue-specific mosaicism, sex chromosome aneuploidies, deformities of hands and feet**

INTRODUCTION

Up to now only one case of proven nonmosaic trisomy 15 has been reported [Coldwell et al., 1981]; however, only one tissue had been examined in this patient. Mosaic trisomy 15 has been reported 4 times, twice accompanied by sex chromosome aneuploidy [Gimelli et al., 1983; Stallard and Sommer, 1989; Bennett et al., 1992; Fryns et al., 1993]. From these cases as well as from a patient of our own, we think that a consistent clinical syndrome can be delineated.

CLINICAL REPORT

M.G., a boy, was the first child of healthy nonconsanguineous parents. The father was 31, the mother 28 years old. The mother has a maternal cousin who is said to suffer from Down syndrome. Otherwise, there are no known physical or mental handicaps in the family history. One year before our patient's birth, the mother had a spontaneous abortion in the 11th week of pregnancy. Pregnancy with our patient was uneventful and the child was born at term after rupture of the membranes 25 hours before birth. Delivery was uncomplicated, birth weight was 3,510 g, length 53 cm, and head circumference 34 cm. A large inguinal hernia was repaired on the third day of his life. At birth, right pes equinovarus and left pes adductus were diagnosed. Both hands showed camptodactyly. They were fixed in a clenched position, digits V overriding digits IV. Digits II showed ulnar deviation, sometimes overriding digit III, sometimes kept hidden under the adducted thumbs. Digits III and IV were held in a windmill position (Figs. 1, 2). There was a cleft between digits II and III bilaterally, a finding said to represent a minimal expression of ectrodactyly, although all fingers were present. The toes showed tibial deviation. Fingernails and toenails were hypoplastic. The child had a large cleft of the soft palate. The following craniofacial anomalies were noted at the age of one month: prominent forehead, large, slightly upturned nose with deep root and broad nasal bridge. Mouth was small with narrow lips, protruding philtrum with a dimple-like groove in the midline. There was mild micrognathia. The ears were well formed and normally positioned. Nipples were widely spaced (Fig. 3). Chest films showed only 11 pairs of ribs. Testes were descended and neurostatus was normal.

Because of bilateral seromucotympanon the patient was adenotomied at age 7 months. At the same time bilateral paracentesis was done. Drainage was applied at the age of 8 months when cleft palate was closed. Lower extremities were treated with cast and surgery. The patient started walking at the age of 14 months. His mental development was normal. Evaluation of heart, lungs, kidneys, intestines, and eyes disclosed no abnormal findings. At the age of 2 years and 2 months he spoke in short sentences and could count up to 10. Micrognathia had disappeared but a slight antimongoloid slant to the eyes was apparent and the eyes appeared deeply set. Surgical corrections of hand malformations were done on several occasions around age 2 years. A funnel chest was noticed and bilateral aplasia of the cruciated ligaments of the knees was diagnosed. Therefore gait was somewhat clumsy.

CYTOGENETIC INVESTIGATION

Of 50 metaphases from cultured lymphocytes analyzed with G-banding, 48 were normal (46,XY). In 2, an extra chromosome 15 was identified, the karyotype being 46,XY/47,XY,+15. A second slide stained for

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Address reprint requests to Professor Erica M. Bühler, M.D., Department of Medical Genetics, University Children's Hospital, Romergasse 8, CH-4005 Basel, Switzerland.

Fig. 1. Patient M.G. at age 4 months. Note postural anomalies of fingers.

Fig. 2. Left hand of patient. Note clenched position, digit V overriding digit IV.

Fig. 3. Front view of patient's face. Note prominent nose and dimple of philtrum.

Q-banding was screened for D-group chromosomes and 2 more metaphases with an extra chromosome 15 were found in about another 50 metaphases. In a second lymphocyte culture established 2 years later, no trisomic cells were found in 100 metaphases examined. But fluorescent in situ hybridization (FISH) analysis with CEP 15 alpha-satellite probe (Imagenetics) showed 5 of 45 interphase nuclei with 3 spots (Fig. 4a).

From a first skin biopsy taken at surgery fibroblast cultures were established and 45 metaphases analyzed. None of them showed trisomy 15. A second fibroblast culture at age 2 years again showed no trisomy 15 in 109 metaphases examined cytogenetically. However, FISH analysis showed 3 of 52 unselected interphase nuclei with 3 spots, indicating trisomy 15. In the disomic cells, often one signal seemed to be smaller than the other. In the trisomic nuclei one signal was bigger than the 2 others (Fig. 4b). Of 16 selected prometaphases not analyzed in detail cytogenetically, 4 had 3 signals (Fig. 4c).

DISCUSSION

Trisomy 15 comprises 7.6% of all trisomic spontaneous abortions [Bennett et al., 1992]. To our knowledge, only 2 cases of full nonmosaic trisomy 15 in a liveborn have been reported [Coldwell et al., 1981; Kuller and Laifer, 1991]. The children died on the fourth day of life and 9 hours after birth, respectively. However, one tissue only had been examined in both. In 100 lymphocyte metaphases from the male reported by Coldwell et al., all had trisomy 15. In 20 metaphases from unknown tissue of the male with hydrops reported by Kuller and Laifer, all were trisomic.

Of 6 cases with proven mosaic trisomy 15, only 3 were diagnosed in living infants, 3 were diagnosed prenatally, and pregnancy was interrupted subsequently [Gimelli et al., 1983; Bennett et al., 1992; Sundberg et al., 1994]. Interestingly, 2 of the living children with mosaic trisomy 15 had, in addition, aneuploidies of sex chromosomes. The boy reported by Stallard and Sommer [1989] had only 45,X cells in cultured lymphocytes and skin fibroblasts. In fibroblasts grown out from his testes, 20% were 47,XY,+15. In the girl described by Fryns et al. [1993], lymphocytes showed a 47,XXX karyotype and skin fibroblasts a 47,XX,+15 karyotype. The third liveborn with mosaic trisomy 15 died at age 13 days [Lähdetie and Lakkala, 1992].

In our patient, 4 of 200 mitoses examined from 2 different lymphocyte cultures showed trisomy 15. In 2 separate skin biopsies no trisomic cells were found. Interphase cells analyzed with FISH showed about 8% of nuclei with 3 signals in both lymphocytes and fibroblasts. In fact, this child is normally developed mentally and has no major organ malformations. His main clinical findings are minor craniofacial anomalies and rather severe deformities of the hands and feet. The most consistently affected organ in full and mosaic trisomy 15 seems to be the nose. It is described as "large," "bulbous," prominent, upturned, with broad, flat nasal bridge or deep nasal root. Further, more or less consistent anomalies are high arched palate, micro- and/or retrognathia, small mouth, short neck, and sternum;

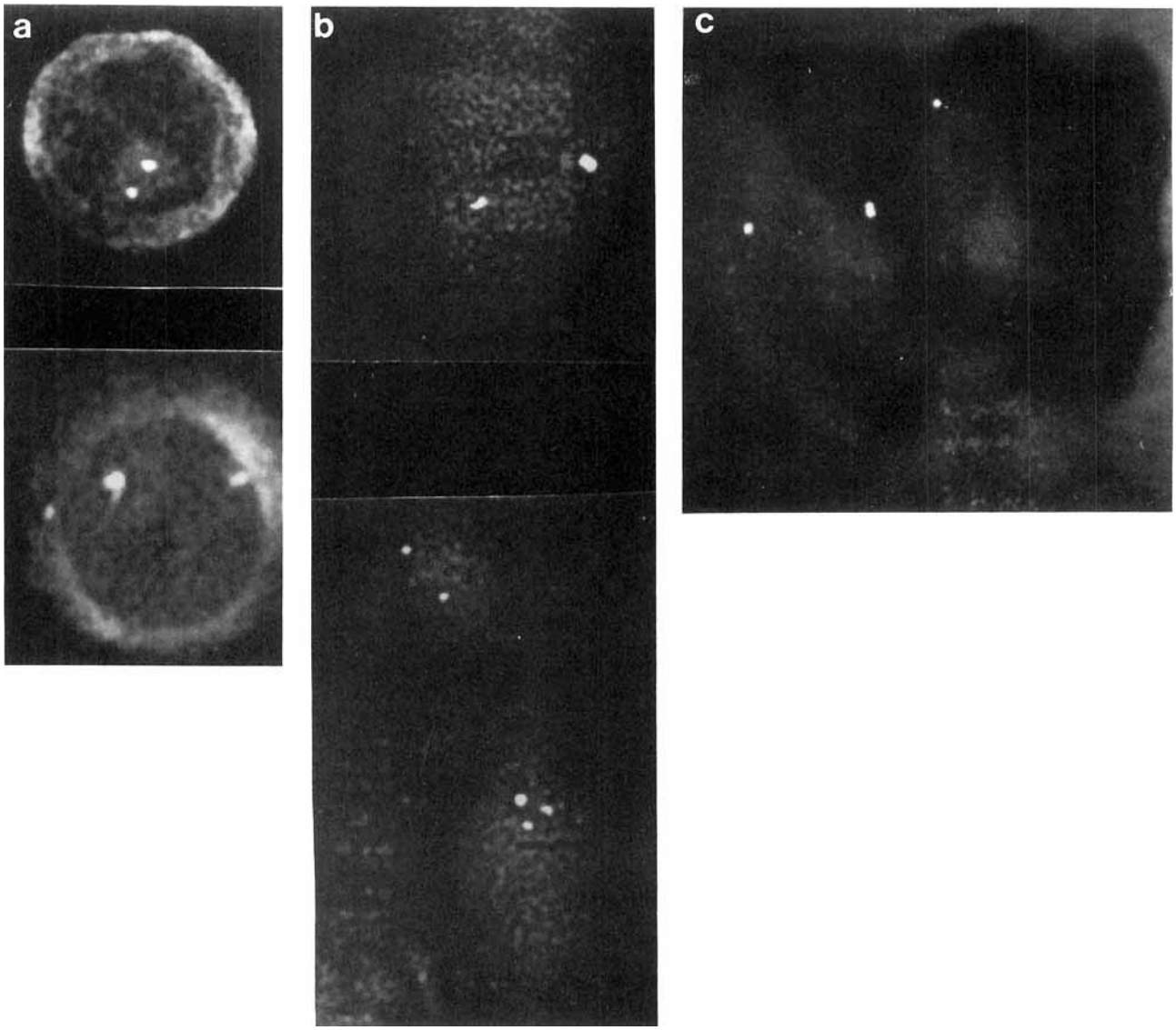

Fig. 4. **a:** Disomic 15 nucleus from lymphocyte culture (top). FISH with CEP 15 alpha-satellite probe (Imagenetics). Trisomic 15 nucleus from lymphocyte culture (bottom). **b:** Disomic 15 nucleus from fibroblast culture (top). Note different size of signals. Disomic and trisomic 15 nuclei from fibroblast culture (bottom). **c:** Trisomic 15 prometaphase. Note one larger and 2 smaller dots.

all nonspecific anomalies occurring in many different chromosomal disorders. Anomalies of the ribs may be common in trisomy 15. Deformities of hands and feet occur rather inconsistently, although they were the prominent features in our patient.

Full mosaic trisomy 15 does not seem to be a more severe clinical condition than partial trisomies or tetrasomies [for review see Schnatterly et al., 1984; Blennow et al., 1994]. This may be due to the normal cell line which in all cases predominated the trisomic line in lymphocyte cultures (see Table I). It seems as if tissue-specific mosaicism was common, as the trisomic cell line in 2 cases was only present in fibroblasts [Stallard and Sommer, 1989; Fryns et al., 1993].

It is possible that mosaic trisomy is often overlooked by clinicians and cytogeneticists alike. Since arthrogryposis-like hand and foot malformations are most striking at birth and require lengthy orthopedic treatment, the craniofacial changes may not be appreciated immediately or even overlooked. As our patient also had a huge inguinal hernia requiring immediate surgery, and a cleft palate requiring close observation initially and intensive nursing care thereafter, attention was soon drawn to the craniofacial anomalies. Likewise, in our patient trisomy 15 was found in lymphocytes, the tissue almost always examined first when a chromosome aberration is suspected. If, as in other cases, the trisomic line is only found in fibroblast cultures, some-

TABLE I. Clinical and Cytogenetic Findings in 6 Individuals with Trisomy 15*

	Coldwell et al. [1981]	Stallard and Sommer [1989]	Kuller and Laifer [1991]	Lähdetie and Lakkala [1992]	Fryns et al. [1993]	Present case
Age at examination	Newborn	6 months	Newborn	Newborn	3 months	1 month
Sex	Female	Male	Male	Female	Female	Male
Developmental delay	+	+	+	+	+	−
Broad nasal bridge	+	+	+[a]	−	+	+
Upturned nose	−	+	−	−	+	+
Large/prominent nose	+	−	+[a]	−	+	+
Small mouth	+	−	+[a]	−	+	+
Micro/retrognathia	+	−	−	−	+	+
High arched/cleft palate	−	+	−	−	−	+
Narrow lips	−	−	+[a]	−	+	+
Abnormal ears	+	−	−	−	−	−
Short or webbed neck	+	−	+ (hydrops)	−	+	−
Widely spaced nipples	+	−	−	−	−	+
Short sternum	+	−	−	−	+	−
Abnormal number of ribs	+ (11)	n.e.	−	−	−	+ (11)
Overriding fingers and/or toes	+	−	−	−	+	+
Clenched hands	−	−	−	−	+	+
Talipes equinovarus	+	−	−	−	−	+
Anteriorly placed anus	+	−	−	−	+	−
Congenital heart defect	+	−	−	+	+	−
Percentage of cells with trisomy 15			100 (20/20) Tissue n.m.			
Lymphocytes	100 (100/100)	0 (0/100)		0 (0/100)	0 (0/35)	2 (4/200)
Skin fibroblasts	n.e.	0 (0/22)		n.e.	100 (36/36)	0 (0/154)
Fibroblasts various organs	n.e.	20 (7/35)		60 (201/336)[b]	n.e.	n.e.
Amniotic fibroblasts	n.e.	n.a.		8 (10/115)	n.a.	n.a.
Other aneuploidies	—	X0	−	−	XXX	−

* n.e. = not examined; n.a. =not applicable; n.m. = not mentioned.
[a] According to picture.
[b] Only extraembryonic tissue.

times in fibroblasts of one organ only [Stallard and Sommer, 1989], the cytogenetic diagnosis may not be established immediately or not at all.

With the advent of in situ hybridization techniques and their increasing application in interphase cytogenetics for diagnosis of chromosome aberrations, the problems of detecting "weak" mosaics may be overcome. One such example is our case where trisomic cells were not detected cytogenetically in skin fibroblasts; only with FISH was trisomy 15 mosaicism confirmed.

FISH should also be applied in patients with Prader-Willi and Angelman syndromes. They, in addition to the typical findings of the respective syndrome, show signs of trisomy 15 (see Table I) because of the known fact that uniparental disomy (UPD) can arise by loss of the "wrong" chromosome 15 from an original trisomic 15 zygote. Since no signs of either Prader-Willi or Angelman syndrome were found in our patient, we did not look specifically for UPD in the predominant disomic 15 cells. Isodisomy could be excluded by the finding of different sizes of alpha-satellite signals in interphase nuclei and by a different amount of centromeric heterochromatin in the 2 chromosomes 15 with C-banding.

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